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EDITORIAL

Intrarenal antibiotic distribution in health and disease

Despite the controversy that exists concerning the exact incidence of pyelonephritis [1], the data of Stamey, Govan and Palmer [2], Reeves and Brumfitt [3], Fairley, Bond and Brown [4, 5] and Ronald, Cutler and Turck [6], identifying the site of infection in urinary tract infections, suggest that 25 to 50% of patients with urinary tract infections may have renal parenchymal infection. The frequency of recurrent urinary tract infections and the fact that a substantial number of all patients entering hemodialysis and renal transplantation programs may have chronic pyelonephritis as their primary form of renal disease serve to document the need for continuing critical evaluation of the management and antibiotic therapy of pyelonephritis.

Although it is reasonable to suspect that tissue antibiotic concentrations may provide an important potential determinant of response to treatment, such data are still somewhat limited. Several different techniques have been used to identify renal tissue drug concentrations; however, each of them possesses distinct limitations which complicate translation of the derived results into solid clinico-therapeutic information.

In pyelonephritis there are unique features of the intrarenal location of infection and the intrarenal distribution of antibiotics that make review of these two phenomena a potentially productive exercise. The site of initial bacterial seeding in acute pyelonephritis and the zone of continued bacterial activity in chronic active pyelonephritis is predominantly the medullary-papillary region of the kidney [2, 7–11]. Although the reasons for this curious susceptibility of the inner zones of the kidney to bacterial infection are incompletely understood, some clear-cut relationships have been identified between both the structural integrity and the functional activity of the kidney and its susceptibility to bacterial infection. It appears that the low blood flow into the medulla and papilla, which is an integral part of the operation of the countercurrent multiplier system [12], may result in decreased delivery of leukocytes, complement and antibody into the inner zones of the kidney, while the reduced tissue oxygen tension and hypertonicity in the latter zones also inhibit leukocyte function and thereby increase tissue susceptibility to infection. The anticomplementary effect of free ammonia in the renal medulla and papilla [8] also enhances the susceptibility of these tissues to bacterial infection.

Recent work from our laboratory indicates that remarkable variation exists among the different antibiotics with respect to the medullary-papillary concentrations achieved during their administration. In addition, the intrarenal distribution pattern of these compounds is often significantly altered as the state of renal physiologic activity is changed, or by the presence of disease in the renal parenchyma. These findings suggest that we should attempt to properly evaluate the potential therapeutic importance of correlating the pathophysiology and antibiotic management of pyelonephritis. To do so we need to ask two fundamental questions: *1*) What are the determinants of renal tissue drug concentration in the presence of normal kidney function? *2*) How does the presence, form and extent of renal disease influence tissue drug accumulation?

An answer to either of these questions must of necessity include information pertinent to *a*) the physiochemical nature of the drug such as its degree of serum and renal tissue protein binding, its molecular size and configuration, its ionization characteristics and degree of lipid solubility; *b*) the extent to which the compound may participate in active transtubular secretory processes, pH-dependent non-ionic diffusion processes or countercurrent exchange processes; *c*) the identification of measured tissue drug levels as being representative of bioactive antibiotic or metabolically degraded drug; *d*) the free bioactive drug concentrations at the critical anatomical site, or distribution volume, in terms of antibacterial activity; *e*) the influence of various forms and extent of renal disease on intrarenal parenchymal drug concentration; and *f*) the significance of drug dosage in influencing kidney tissue drug accumulation in either healthy or diseased kidneys.

For many antibiotics comprehensive data as listed

above are often unavailable, or at best the information is fragmentary. However, from a practical point of view we can coalesce and briefly review data derived using four investigative techniques that are particularly suited to identifying intrarenal drug pharmacokinetics in health and disease: *1*) analysis of renal lymph, *2*) autoradiography and fluorescence distribution in renal tissues, *3*) stop-flow studies and *4*) analysis of renal tissue homogenates.

Renal lymph analysis. Since lymph fluid represents a derivative of interstitial fluid, analysis of antibiotic concentrations in renal lymph represents a method of defining antibiotic concentrations in the interstitial fluid of the kidney [13–18]. In such studies it is assumed that cortical drug concentrations are reflected in the lymph obtained from capsular lymphatics and that hilar lymph reflects interstitial concentrations of drug in the medulla and papilla. However, recent studies of lymph formation in the kidney [19, 20] indicate that it is not possible to separately identify lymph produced in the interstitium of the renal medulla-papilla and that of the cortex.

Autoradiography and fluorescence distribution in the kidney. Autoradiographic techniques have been used to evaluate renal tissue concentrations of streptomycin and tetracycline by Andre [21] and by Currie, Little and McDonald [22] to study cephaloridine and nitrofurantoin. Similar techniques were used by Romas and Clark [23] to evaluate tetracycline concentrations in healthy and pyelonephritic rat kidneys. These studies have proved of some value in identifying the intrarenal distribution and cellular location of the above-named drugs; however, quantitative data cannot easily be derived from the investigations, and the state of hydration and urinary pH of the experimental animals were not clearly identified. Most importantly, from the therapeutic point of view, such studies only identify a tissue concentration of radioactivity which could represent both microbiologically active antibiotic and nonbioactive radioactive metabolites of the drug.

Helander and Bottinger used the fluorescent properties of the tetracycline analogues under ultraviolet light to monitor the tissue distribution of those compounds in the kidneys of mice [24]. Subsequently, Malek et al [25] described the distribution of tetracycline analogues in experimentally diseased rabbit kidneys and demonstrated that tetracycline fluorescence was particularly prolonged in areas of ischemic renal parenchyma. The drawback to the use of fluorescent techniques is similar to that noted for radioautography, since microbiologically active, complexed and inactive tetracycline degradation products cannot be separately identified within the tissues.

Stop-flow studies. Stop-flow analysis may be useful in identifying the site of antibiotic secretion or reabsorption within the nephron. However, only a small number of antibiotics have been investigated by such means. In the case of nitrofurantoin (pKa 7.2) Woodruff, Malvin and Thompson [26] used stop-flow studies to demonstrate that the drug was influenced distally in the nephron by urinary pH, with the greatest degree of distal tubular reabsorption occurring when the urine was acid and highest urine concentrations of the drug being apparent when the urine was alkaline. Cephaloridine transport by dog and rabbit nephrons was investigated by Child and Dodds [27]. They interpreted their results as showing that cephaloridine was not secreted by the proximal tubule in such species and thereby raised some important questions concerning the nephrotoxicity of the drug, since its presumed nephrotoxicity was postulated as being related to proximal tubular secretion. The subsequent studies of Tune [28] clearly identified the importance of proximal tubular secretion of cephaloridine in rabbit kidney, particularly with respect to its nephrotoxicity, and his important studies will be reviewed in more detail later. These contradictory studies of the renal handling of cephaloridine identify the care with which stop-flow results must be interpreted, since in such studies the measured urinary concentration of drug may represent the net result of unidirectional or bidirectional active secretion in the proximal tubule with or without distal tubular reabsorption.

Intrarenal ampicillin (pKa_1 2.7; pKa_2 7.5) pharmacokinetics have been studied in our laboratory [29] by stop-flow analytic techniques and will be discussed later.

Analysis of renal tissue homogenates. Most pharmacologic screening of antimicrobial compounds defines drug concentrations in homogenates of whole kidney, and only in a small number of investigations have tissue concentrations of antimicrobials been measured in the different zones of the kidney.

The intrarenal distribution of several drugs in the sulfonamide class have been studied by direct analysis of renal tissue homogenates for sulfonamide activity. The studies of Schlegel and Burden [30] and O'Dell, Jarrell and Schlegel [31] in the dog kidney have shown that although the state of hydration could markedly change the concentrations of sulfurazole or sulfisoxazole in the urine, the renal tissue levels of drug were only slightly increased in the hydropenic state. Silva, Macia and Torretti [32] found similar results for sulfisoxazole in hydropenic rat kidneys, and Silva and Mudge [33] demonstrated that, in dog kidney, sulfasymazine medullary-papillary concentrations were

only slightly increased during antidiuresis, but that despite a pH-dependent renal clearance distal non-ionic diffusion did not influence renal tissue concentrations of the drug.

In our laboratories this technique of antibiotic analysis in renal tissue homogenates has served to define the intrarenal distribution characteristics of several of the commonly used antibiotics and the influence of the state of hydration and urinary pH upon the latter gradient patterns [34–39].

Intraluminal location of drug versus interstitial and intracellular location. Total antibiotic concentrations measured in renal tissue homogenates represents a sum of contributions from blood, interstitial fluid, intracellular fluid and intraluminal filtrate or urine. No exact data are available to define the anatomic volume of renal tissue occupied by intraluminal contents in either the cortex, medulla or papilla of the kidney. We have previously, however, made some estimate of the volume of papilla occupied by intraluminal contents during hydropenia by comparing distribution volumes of different substances [35]. From such data and from our unpublished studies characterizing the intrarenal distribution characteristics of inulin and *p*-aminohippuric acid it appears that approximately 1.4 to 2.0% of the hydropenic normal papilla is occupied by intraluminal urine.

In the case of the commonly used antibiotics it is also possible to define a theoretic volume of drug distribution in the hydropenic papilla. When the latter volume is greater than the anatomic confines of the intraluminal space, the excess of the antibiotic distribution space must represent the quantity of drug distributed in the interstitial (including vasa recta blood) and intracellular spaces of the hydropenic papilla. For example, in the case of carbenicillin (37) the drug's theoretic papillary volume of distribution may be calculated as follows:

$$\frac{\text{Carbenicillin conc/ml}_{\text{hydropenic papilla}} \times 100}{\text{Carbenicillin conc/ml}_{\text{urine}}} = 4.2 \pm 0.5\%$$

Comparable figures for ampicillin, inulin and *p*-aminohippuric acid are 1.4 to 2.0%. If this lower distribution volume range is taken as that most closely approximating the anatomic intraluminal volume, then it may be estimated that one-half to two-thirds of the measured carbenicillin in the hydropenic papilla is distributed outside the lumina of those portions of nephron included in the papilla. It thus appears that papillary concentrations of carbenicillin exceed that of plasma by as much as 12 to 15 times. Although this value of carbenicillin concentration within the interstitial-intracellular areas of the normal hydropenic papilla represents an approximation, it nonetheless identifies an order of magnitude for compartmental distribution of the drug in the renal papilla and affords a useful means of interpreting the results of intrarenal drug distribution characteristics when papillary tissue homogenates of drug are measured.

These data also suggest that consideration of this type may be of major importance in determining the usefulness or effectiveness of different antibiotics, particularly with respect to correlating bacterial drug sensitivity data identifying the minimal inhibitory concentrations of the compound and the drug levels achievable in different zones of the kidney at specific dosage regimens.

Factors influencing intrarenal antibiotic distribution in normal kidneys. It is not practical to review here all of the determinants influencing drug accumulation and distribution in the healthy kidney. However, it is worthwhile to take a broad view of the influence of the state of hydration, the significance of antibiotic binding to renal tissue and the role of urinary pH in determining the intrarenal distribution characteristics of antibiotics.

Influence of the state of hydration. Data on antibiotic concentrations in normal kidneys have been obtained in experimental animal models, in particular the dog. Fig. 1 summarizes the influence of the state of hydration upon the intrarenal gradient patterns of several of the more commonly used antibiotics as determined in 186 healthy dog kidneys by techniques previously described from this laboratory [35]. In these studies the hydrated and hydropenic states represented, respectively, urine flow rates of 2 to 4 ml/min/kidney (urine osmolality 200 to 300 mOsm/kg) and 0.1 to 0.05 ml/min/kidney (urine osmolality 1000 to 2000 mOsm/kg). The urine/serum ratios in hydropenia were greater than 500 in the case of penicillin G and carbenicillin; 200 to 300 for ampicillin, gentamicin, kanamycin and cephalothin; 50 to 150 for oxytetracycline and sulfisoxazole; and in the case of doxycycline the ratio was 15. None of these urine/serum ratios have been corrected for serum protein binding. They clearly indicate, when compared to the renal tissue/serum concentration ratios, that urinary concentrations of an antibiotic do not necessarily directly reflect concomitant drug concentrations in the medulla-papilla of the kidney, and thereby resolve a point of earlier controversy [2]. In the hydrated state the urine/serum ratios ranged between 5 and 15 for all antibiotics except oxytetracycline and doxycycline, where the ratios were 2 and 1, respectively.

For the penicillins and cephalothin, a significant increase in cortico-papillary gradient pattern is noted in the hydropenic state with drug concentrations following the sequence penicillin G > carbenicillin >

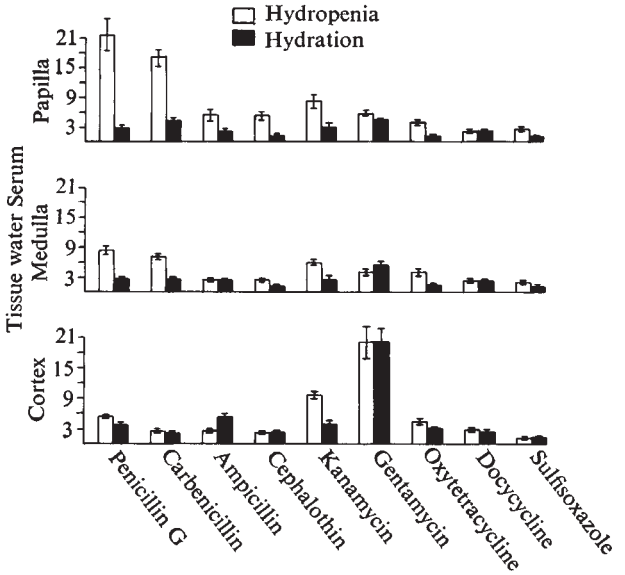

Fig. 1. *Intrarenal gradient patterns of many commonly used antibiotics in 186 healthy dog kidneys during variation in the state of hydration.* Concomitant urine/serum ratios are included in the text.

ampicillin = cephalothin. When the volumes of distribution of these compounds in the hydropenic papilla are measured as described earlier, the increase in antibiotic concentration in the interstitial-intracellular region of the papilla over that measured concomitantly in the serum is ten to 15-fold in the case of penicillin G and carbenicillin; three to six-fold for cephalothin and for ampicillin with alkaline urine; and one and one-half to three-fold for the remaining drugs in Fig. 1.

It is apparent that in the hydrated state (Fig. 1) the increase in cortico-papillary gradient noted for the penicillins and cephalothin during hydropenia is completely ablated. This "wash out" of antibiotics from the renal tissues is also associated with markedly decreased urinary drug concentrations. The other remaining antibiotics in Fig. 1 do not exhibit significant increases in cortico-papillary distribution pattern during hydropenia, although an overall increase in tissue drug concentration during hydropenia is of note for kanamycin, oxytetracycline and sulfisoxazole.

Renal tissue drug binding. A most important additional finding was the observation of a 20-fold increase in cortical gentamicin concentrations over those noted in the serum. The renal lymph studies of Chisholm, Calnan and Waterworth [16, 17], however, demonstrated that gentamicin concentrations in the latter fluid were similar to concomitant serum values. Since gentamicin accumulation in the renal cortex may bear some relationship to its potential nephrotoxicity, this observation was explored further. In the cortex we identified a 70 to 85% binding of the drug to cellular proteins. This reconciles our results with the renal lymph studies of Chisholm et al [16, 17], since the fraction of gentamicin found in the renal cortex could not be detected by renal lymph analysis. In addition our preliminary data have demonstrated, in half of the dogs studied, that quinine, a blocker of the proximal tubular organic base secretory system [40], significantly reduced cortical gentamicin accumulation.

One possible explanation for the high cortical gentamicin concentration is the diffusion or transport of this highly charged basic aminoglycoside antibiotic into the proximal tubular cells, with intracellular binding of the drug to proteins of opposite charge. By comparison it is noteworthy that concentrations of the nephrotoxic cephalosporin cephaloridine in rabbit renal cortex as measured in the studies of Tune [28] were twelve times those noted in the serum. The latter drug is a derivative of an organic acid, and the administration of competitive blockers of the organic acid proximal tubular secretory system not only reduced the renal cortical concentrations of cephaloridine but also protected the kidney against the nephrotoxic effects of the compound. It is also evident (Fig. 1) that hydropenic cortical concentrations of the aminoglycoside kanamycin are some ten times those noted in serum. These data suggest that additional investigations of renal tissue binding of nephrotoxic drugs may further contribute to an understanding of the mechanisms of their nephrotoxicity.

Influence of urinary pH. Since most antibiotics are either weak acids or bases, it might be expected that many of them would be influenced in both renal clearance and renal tissue concentration by inducing changes in urinary pH through the mediation of the physiologic phenomenon of non-ionic diffusion [40]. Woodruff et al [26] demonstrated by stop-flow analysis that furadantin (pKa 7.2) undergoes distal non-ionic diffusion with higher clearance values associated with alkaline urine. Unfortunately, concomitant tissue analyses were not performed in their studies. Studies from our laboratory demonstrated a pH-dependent clearance for the organic acids, penicillin G and cephalothin [34] and identified an influence of urinary pH [29] on the intrarenal distribution characteristics of ampicillin (pKa_1 2.7; pKa_2 7.5). Alkaline urine significantly increased medullary-papillary concentrations of ampicillin. Stop-flow analysis revealed that during production of alkaline urine there was an enhancement of proximal tubular secretion of the compound, such as has been demonstrated for *p*-aminohippuric acid during systemic alkalosis [41], and that as ampicillin reached the distal portion of the

nephron it underwent greater non-ionic back diffusion into interstitium of the medulla and papilla than was seen during production of acid urine. Thus, an intrarenal recycling of the drug occurred during the production of alkaline urine.

Sulfisoxazole (pKa 4.9) renal tissue concentrations are not much influenced by the state of hydration (Fig. 1), but relative concentration of the drug in the medulla and papilla is enhanced during the production of acid urine. Doxycycline (isoelectric point at pH 5.5) demonstrates significant pH-dependent urinary clearance values with enhanced excretion in alkaline urine. The renal tissue concentrations are not, however, influenced by such changes in urinary pH [39].

Antibiotic concentrations in diseased human kidneys. Gradient patterns of several antibiotics in the diseased renal tissues of patients with end-stage kidney disease have been studied as such individuals were undergoing bilateral nephrectomy in preparation for renal transplantation. The patients received the usual parenteral therapeutic doses of an antibiotic two to four hours prior to nephrectomy. Table 1 summarizes data derived from these studies in 37 diseased human kidneys and contrasts the results with comparable figures for normal hydropenic dog kidneys. Since adequate urinary specimens could not be obtained at nephrectomy, urine/plasma drug data at similar dosage schedules were collected one week prior to nephrectomy for comparison with the renal tissue data. These urine/plasma ratios ($\pm$ SEM) were gentamicin 3.1 ± 1.3, carbenicillin 11.3 ± 2.4, ampicillin 3.5 ± 0.8, cephalothin 1.0 ± 0.2 and doxycycline 0.6 ± 0.08.

With the exception of doxycycline, a significant reduction of antibiotic concentration was produced in each zone of the diseased kidney tissue when compared with healthy kidneys. The tissue drug concentrations tend to be the same in each zone of the kidney and are in general approximately one-half to two-thirds the concomitant serum value. In the case of doxycycline tissue, values remained some twofold higher than concomitantly measured serum levels. It would therefore appear that serum antibiotic levels represent the best guide to coexistent drug levels in diseased renal tissue. It is again important to emphasize that no data are available to correlate solidly these drug concentration results in severely diseased human kidneys with either short- or long-term therapeutic results. The drug concentration data taken on their own perhaps suggest that in the management of patients with diseased and infected kidney tissues it may be more therapeutically desirable to select a compound with the least systemic toxicity and the most effective tissue accumulation. This fundamentally important question deserves much further attention and evaluation so that solid clinico-therapeutic correlates can be developed.

Two additional studies of the concentrations of carbenicillin and naladixic acid in diseased human kidneys are of note. Ivan, Arr and Foldi [42] reported on the carbenicillin concentrations achieved in whole renal tissue at a time when unilateral nephrectomy was undertaken for the management of pyelonephritis or renal tumor, although preoperative renal function and state of hydration were not reported. The renal tissue/plasma ratio of carbenicillin was $3.2 \pm$ SEM 0.3 at the time of nephrectomy. Penetrance of the drug into tumorous tissue, analyzed separately, was markedly reduced. Jameson [43] studied nalidixic acid concentration in diseased renal tissue obtained from patients undergoing elective nephrectomy for pyelonephritis. Mean renal tissue drug concentrations were two and one-half times those noted in serum, but the preoperative renal function was not recorded.

The data presented in Fig. 1 and Table 1 represent opposite ends of a spectrum of antibiotic concentration in healthy and diseased kidneys. Further information will be necessary to characterize the drug concentrations in renal tissue that may be achieved at

Table 1. Renal tissue/serum ratios for healthy hydropenic dog (56 studies) and diseased human kidneys (37 studies)[a]

	Cortex		Medulla		Papilla	
	Healthy	Diseased	Healthy	Diseased	Healthy	Diseased
Gentamicin	20 ± 2.4	0.9 ± 0.08	4 ± 0.6	0.9 ± 0.09	6 ± 0.3	0.8 ± 0.08
Kanamycin	10 ± 0.7	0.5 ± 0.05	6 ± 0.5	0.5 ± 0.07	8.5 ± 1.0	0.5 ± 0.08
Carbenicillin	3 ± 0.3	0.6 ± 0.1	7 ± 0.7	0.7 ± 0.05	18 ± 1.3	0.7 ± 0.06
Ampicillin	2.7 ± 0.4	0.5 ± 0.07	2.6 ± 0.5	0.7 ± 0.3	5.7 ± 0.9	0.5 ± 0.07
Cephalothin	1.9 ± 0.2	0.6 ± 0.3	2.6 ± 0.3	0.6 ± 0.2	5.7 ± 0.6	0.6 ± 0.2
Doxycycline	3 ± 0.3	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.3	2.0 ± 0.1	2.0 ± 0.2

[a] Mean $\pm$ SEM.

intermediate degrees of renal impairment. An appropriate model of experimental pyelonephritis could provide the means of obtaining such results.

Summary. The major points of potential therapeutic importance deriving from the study of intrarenal antibiotic distribution characteristics may be summarized as follows: *1*) It is difficult to predict the intrarenal distribution characteristics of an antibiotic since factors other than plasma concentration and antibiotic clearance by the kidney appear to exert significant influences upon accumulation within different regions of the kidney. *2*) The hydropenic state enhances the cortico-papillary gradient pattern of several antibiotics, particularly the penicillins, cephalothin and to a lesser extent the sulfonamides. *3*) Induction of the hydrated state serves to reduce markedly the urinary concentrations of all antibiotics; in addition the penicillins, cephalothin, kanamycin, oxytetracycline and the sulfonamides are reduced in or "washed out" from the renal parenchyma during water diuresis. *4*) Alkaline urine facilitates an increase of ampicillin concentrations in the renal medulla and papilla; acid urine increases the distribution of sulfisoxazole in the latter zones. Several antibiotics demonstrate pH-dependent renal clearance. *5*) Contrary to previously held concepts, the urinary concencentration of an antibiotic does not necessarily reflect the coexistent drug level in the renal medulla or papilla. *6*) The presence of severe disease in the renal parenchyma significantly changes the intrarenal pharmacokinetics of antibiotics and is associated with reduced tissue concentrations of all drugs with the exception of doxycycline. *7*) No clinical data are as yet available to correlate drug distribution in healthy or diseased renal tissue with long term therapeutic results. Such studies merit careful attention.

Intrarenal tissue drug distribution studies may ultimately provide a better understanding of the factors of importance in selecting the appropriate drug for treatment of renal infections and may contribute to a better understanding of the mechanisms underlying antibiotic nephrotoxicity. Data available at present are incomplete and often fragmentary, but further systematic study of the factors influencing intrarenal drug concentrations promises information of both therapeutic and toxicologic value.

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